REMARKS

Status of the claims

Claims 26, 30 and 31 are pending in the application. Claim 31 is currently amended. Claims 26, 30-31 are rejected.

Claim amendment

Claim 31 has been amended to delete the term "suspected or at risk of having cancer". This amendment has been incorporated to overcome rejection of claims 30-31 under 35 USC §112, first paragraph.

Claim rejection under 35 USC 112, first paragraph

Claims 26 and 30-31 are rejected under 35 USC §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, to make and use the invention commensurate in scope with these claims. Applicant respectfully traverses this rejection.

The Examiner states that the specification provides for producing activated T cells directed towards human stratum corneum chymotrytic enzyme (SCCE). The Examiner contends that the specification however does not provide for a method to reintroduce activated dendritic cells into an individual that has or is suspected of having or is at risk of getting ovarian or prostrate cancer. Applicant respectfully disagrees.

Applicant submits that cell based therapy to treat malignant and non malignant conditions were known at the time the instant invention was made and disclosed. Dhodapkar et al. (reference enclosed) teaches the injection of mature antigen-pulsed human dendritic cells (DCs) in human volunteers. The DCs were pulsed with two foreign proteins, keyhole limpet hemocyanin and taetanus toxoid and an HLA A2.1-restricted influenza matrix peptide. The dendritic cells were found to rapidly elicit $CD4^+$ and $CD8^+$ cell immunity in vivo. Thus prior art not only teaches introducing dendritic cells in an individual but also demonstrate that these cells were able to elicit the desired response. It is well established that what is known in the art should preferably not be included in the specification. Thus, the activated dendritic cells can be reintroduced in the body of an individual in need of such cell therapy by methods known in the related art and does not require undue experimentation. There a number of dendritic cell based vaccines for cancer that are in various stages of clinical trials, such as for example dendritic vaccine for multiple myeloma and for melanoma. This indicates that methods to reintroduce dendritic cells in the body are well established.

The Examiner further states that the claims broadly encompass methods of immunotherapy targeted towards human stratum corneum chymotrytic enzyme in an individual comprising isolating dendritic cells from said individual, exposing the dendritic cells to the stratum corneum chymotrytic enzyme protein encoded by SEQ ID NO: 30 or the stratum corneum chymotrytic enzyme peptide selected from SEQ ID NOS: 31, 32, 33, 34, 35, 36, 80, 86 and

99 and reintroducing said activated dendritic cells into said individual wherein the activated dendritic cells activates stratum corneum chymotrytic enzym-specific immune responses in said individual, wherein the individual has cancer, is suspected of having cancer or is at risk of getting cancer, wherein the cancer is selected from ovarian or prostrate cancer, which broadly encompasses preventing cancer. The Examiner further states that the Applicant has only demonstrated that human SCCE 9-mer peptides corresponding to amino acid residues 5-31 and 123-131 of the human stratum corneum enzyme were effective at inducing specific $CD8^+$ CTL responses in vitro. The Examiner contends that as such, neither the specification nor the Applicant's declaration (filed 19 February 2003) teach that the stratum corneum chymotrytic enzyme peptides consisting of SEQ ID Nos: 31, 34, 80 or 99 are effective at inducing $CD8^+$ CTL responses either in vitro or in vivo. Applicant respectfully disagrees.

Applicant submits that methods for identifying peptides useful for immune stimulation are well known and generally available to one of ordinary skill in the art. For example, 9-mer to 11-mers of the stratum corneum chymotrytic enzyme protein containing binding motifs for HLA class I molecules can be identified using computer programs readily available to one of skill in the art. The binding of these peptides to the top HLA haplotypes in the general population can be analyzed by computer program found on the web site of the National Institutes of Health (http://www.bimas.dcrt.nih.gov/molbio/hla_bind). The program analyzes these peptides based on the predicted half-life of each peptide's binding to a particular HLA allele. A long half-life indicates that the

peptide has strong association with a particular HLA molecule. The stratum corneum chymotryptic enzyme peptides that strongly bind to an HLA allele are putative immunogens. The claimed peptides of SEQ ID Nos. 31, 32, 33, 34, 35, 36, 80, 86 and 99 are determined to contain binding motifs for HLA class I molecules using the method as described supra.

Applicant has demonstrated that peptides of SEQ ID NOS 32 and 33 were effective at inducing specific $CD8^+$ CTL responses in vitro. It is well established that a patent need only demonstrate the application of the invention via some examples. The applicability of all disclosed species is not required to be individually demonstrated or disclosed in the specification. Furthermore the declaration by the Applicant also provides a method for testing the immunogenicity of stratum corneum chymotrytic enzyme peptides. Thus testing the claimed stratum corneum chymotrytic enzyme peptides for their effectiveness at inducing $CD8^+$ CTL responses does not require undue experimentation. Accordingly, Applicant submits that the claims 26 and 30-31 are not broad in encompassing the peptides consisting of SEQ ID NOS: 31, 32, 33, 34, 35, 36, 80, 86 and 99. Accordingly, in view of the arguments and the amendment presented above, claims 26 and 30-31 now recite methods enabled by the specification. Furthermore, claim 26 does not recite a method to treat cancer but rather a method to elicit an immune response against stratum corneum chymotrytic enzyme. As stratum corneum chymotrytic enzyme is overexpressed in ovarian and prostate cancer, it is evident that an individual having or at risk of

having ovarian cancer or prostate cancer will benefit from the method of claim 26.

The Examiner further states that the art of **Hansson et al** (the Journal of Biological Chemistry, 269(30): 19420-19426, 1994) teach the human stratum corneum chymotrytic enzyme polypeptide, which contains a signal peptide of 22 amino acids and a propolypeptide of 7 amino acids followed by the active enzyme. The Examiner further states that the claimed stratum corneum chymotrytic enzyme peptides consisting of SEQ ID NOS: 33, 35, 36 and 86, which reside in the signal peptide are not part of the active stratum corneum chymotrytic enzyme enzyme as the signal peptide is cleaved from the native human stratum corneum chymotrytic enzyme, indicating the unpredictability as it pertains to in vivo immunotherapy directed against the stratum corneum chymotrytic enzyme signal peptide. Applicant respectfully disagrees.

Applicant submits a declaration under 37 C.F.R. §1.132 to demonstrate that CTL activation and CTL recognition of tumor cells does not require use of peptides derived from the active stratum corneum chymotrytic enzyme enzyme. Figure 1 in the declaration clearly shows that CAOV3 ovarian cancer cells that were not pulsed initially with the stratum corneum chymotrytic enzyme peptide of SEQ ID NO: 33 (amino acids 5-13, which resides in the stratum corneum chymotrytic enzyme signal peptide) are lysed in the presence of stratum corneum chymotrytic enzyme-5-13 peptide specific $CD8^+$ cytotoxic T cells. This result provides strong evidence that the stratum corneum chymotrytic enzyme-5-13, which is a part of the stratum corneum chymotrytic enzyme signal peptide is

naturally expressed, processed and presented by ovarian tumor cells. Thus in vivo immunotherapy using signal peptides of SEQ ID NOS: 33, 35, 36 and 86, which are determined to contain binding motifs for HLA class I molecules using the method as described supra cannot be considered as unpredictable. Accordingly the specification enables the use of these peptides for immunotherapy against ovarian cancer.

The Examiner further states that **Roitt** et al teaches that peptide sizes of 12-15 residues are optimal for binding MHC class I molecules and that finding a peptide that binds to MHC molecules and stimulates immune response is not a trivial matter (Wang et al., US Patent 5,840,839). The Examiner also states that it is known that all the factors in T cell stimulation have not been elucidated and that all peptides of similar size derived from the same parent polypeptide are not capable of interacting with T-cells (Bixler et al. U.S. patent 5,785,973 and Geysen, U.S. patent 5,539,084). The Examiner further states that the prior art nor the instant specification teach the full scope of the stratum corneum chymotrytic enzyme proteins and the myriad of fragments thereof for activating T cells toward stratum corneum chymotrytic enzyme for immunotherapy in patients with a reasonable expectation of success. Applicants respectfully disagree.

Applicant would like to respectfully point out that **Roitt** et al. teaches that self peptides eluted from MHC class I molecules have been purified and sequenced and were shown to be nine amino acids in length. **Roitt** et al further teaches that this length contrasts with the size of synthetic peptides i.e.

about 12-15 amino acids that is known to be optimum. Figure 7.22 in **Roitt** et al shows that the peptide residing in the binding groove is about 9 amino acids long and the legend in figure 7.23 states that the binding site on class II molecules accommodates longer peptides than on class I. Thus **Roitt** et al. does not teach that the optimal peptide length for binding MHC class I molecules is between 12-15 amino acids. Applicant further submit that the claimed peptides of SEQ ID Nos. 31, 32, 33, 34, 35, 36, 80, 86 and 99 are determined to contain binding motifs for HLA class I molecules using the method as described supra. Furthermore these peptides are selected on the basis of a computer program that was not used in any of the prior art cited by the Examiner. **Geysen** used all possible 9-mers and 12-mers of the MPB70 sequence to test for T-cell proliferation (col. 2, lines7-9). The peptides used by **Wang** were prepared based solely on the binding motif of HLA-A31 (col. 19-20) and not on the basis of a computer program that takes into account affinity binding kinetics such as the program used in the instant application. Thus it would be inappropriate to assume that the method used by the Applicant will not correctly recognize molecules that can bind HLA class I molecules, especially, in view of the fact that two such peptides (SEQ ID Nos: 32 and 33) were shown to bind HLA class I molecules and activate SSCE-specific T cells. Furthermore, claim 26 does not encompass a myriad of peptides but only encompasses 9 peptides (SEQ ID Nos. 31, 32, 33, 34, 35, 36, 80, 86 and 99) and the polypeptide encode by DNA of SEQ ID NO: 30. One of skill in the related art can use the SCCE protein (encoded by DNA of SEQ ID NO: 30) or the peptides disclosed herein to

generate activated T cells directed towards the SCCE polypeptide using dendritic cells with a reasonable expectation of success based on the specification and what is known in the prior art. Furthermore one skilled in the art can recognize that an individual who can benefit from immunotherapy based on this strategy is an individual with ovarian cancer as SCCE protein is overexpressed in ovarian cancer.

In view of the amendments and arguments presented above, it is evident that the instant specification and what is known in the related art adequately enables claims 26 and 30-31. Accordingly, Applicant respectfully requests that the rejection of claims 26 and 30-31 under 35 U.S.C. 112, first paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed July 25, 2005. Applicant submits that claims 26, 30 and 31 are in condition for allowance and respectfully request that claims 26, 30 and 31 be passed to issuance. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Should any fees be due, please debit Deposit Account No. 07-1185 upon which the undersigned attorney is allowed to draw.

Pursuant to 37 C.F.R. §1.136(a), Applicant hereby petitions that the period for response to the Office Action mailed, July 25, 2005, in the above-referenced application, be extended for three (3) months to and including January 25, 2006. Please credit the $510 extension fee under 37 C.F.R.

§1.17(a) to the credit card identified on the enclosed Form PTO-2038. In the absence of Form PTO-2038, please debit any fees from Deposit Acct. No. 07-1185.

Respectfully submitted,

Date: Jan 20, 2006

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
Tel: (713) 270-5391
Fax: (713) 270-5361
BADLER1@houston.rr.com

Benjamin Aaron Adler, Ph.D.,J.D.
Registration No. 35,423
Counsel for Applicant